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Effect of partial preservation versus complete preservation of Denonvilliers' fascia on postoperative urogenital function in male patients with low rectal cancer (PREDICTION): protocol of a multicentre, prospective, randomised controlled clinical trial

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ABSTRACT

Introduction Total mesorectal excision (TME) has been the gold standard for the surgical treatment of mid-low rectal cancer, but traditional TME removal of Denonvilliers' fascia (DVF) is too low and is prone to damage the connecting branches of the bilateral neurovascular bundles, which can lead to posturogenital dysfunction. A recently published multicenter randomised controlled trial revealed that TME with complete preservation of DVF (CP-DVF) has protective effects on postoperative urogenital function for male patients with rectal cancer with specific staging and location (preoperative staging T1-4N0-2M0, but T1-2 for anterior rectal wall). Our previous studies have confirmed that TME with partial preservation of DVF (PP-DVF) could also achieve satisfactory results regardless of the circumferential location of the tumour. However, there is a lack of randomised controlled trials to prove that the efficacy of TME with PP-DVF is equivalent to that with CP-DVF with respect to postoperative urogenital function.

Methods and analysis This study is a prospective, multicentre, equivalent design, open-label randomised clinical trial in which 278 male patients with low rectal cancer will be recruited from 11 large-scale gastrointestinal medical centres in China. Patients will be randomly assigned to undergo PP-DVF or CP-DVF. We will test the hypothesis that PP-DVF is similar to CP-DVF with respect to sexual function at postoperative month 12 (5-item version of the International Erectile Function Index Questionnaire and ejaculation function classification). The secondary outcomes include the assessment of urinary function, surgical safety and oncological outcomes.

Ethics and dissemination This trial has been approved by the Institutional Review Board of Fujian Medical University Union Hospital (2020YF016-01) and is filed on record by all other centres. Written informed consent will be obtained from all eligible participants before enrolment. The trial's results will be disseminated via peer-reviewed scientific journals and conference presentations.

Trial registration number ChiCTR2000034892.

Strengths and limitations of this study

- This is the first multicentre randomised trial on this topic.
- This study is a prospective multicentre randomised controlled trial that increases the external validity of the findings.
- An essential strength of this study is its applicability in daily clinical practice, as well as the pragmatic nature of the study.
- The main limitation in this study is that it will be relatively difficult to complete the recruitment quickly because factors such as age and neoadjuvant therapy affect preoperative urogenital function.

INTRODUCTION

Rectal cancer is one of the most common cancers worldwide.[1] The principle of total mesorectal excision (TME) proposed by Heald *et al*[2] has now become the gold standard for the surgical treatment of mid–low rectal cancer, reducing local recurrence rates and improving long-term survival.[3] However, more than 50% of patients have urogenital dysfunction after traditional TME,[4 5] which significantly reduces the quality of life of these patients. Injury of the pelvic autonomic nerve (PAN) during TME is the most important factor of postoperative urogenital dysfunction. Therefore, preservation of postoperative urogenital function by modifying the surgical approach for TME has attracted much attention.

Traditional TME requires dissection in front of Denonvilliers' fascia (DVF), while bilateral neurovascular bundles (NVB) are located anterior to the lateral sides of the

DVF. To avoid intraoperative damage to the NVB, an 'inverted U-shaped' excision of the DVF just above the point of adherence of DVF to the back of the prostate was proposed by Heald *et al*[6] in 2003. Although oncological outcomes are satisfactory,[7] postoperative erectile dysfunction occurs in up to 40%–77% of patients, and the incidence of ejaculation dysfunction is 28%–42%.[8 9] Because the excision level of the DVF is too low, it may damage the connecting branches of the bilateral NVB.

Recently, dissection behind the DVF, TME with complete preservation of the DVF (CP-DVF), was proposed by some researchers.[10 11] A recently published multicentre randomised controlled trial[12] revealed that CP-DVF has protective effects on postoperative urogenital function for male patients with rectal cancer with specific staging and location (preoperative staging T1-4N0-2M0, but T1-2 for anterior rectal wall). However, it is still controversial whether this surgical procedure is suitable for advanced tumours of the anterior rectal wall. Moreover, we found that the DVF was closely fused with the proper fascia of the rectum at the lowest level of peritoneal reflection.[13] CP-DVF by incision at the lowest level of peritoneal reflection may have difficulty ensuring the integrity of the proper fascia of the rectum.

Based on a better understanding of the anatomy and histology between the DVF and NVB,[13 14] we have proposed dissection in front of the DVF with partial preservation (PP-DVF).[13 15–17] Briefly, the dissection commences at 1 cm above the peritoneal reflection, ensuring that the surgical plane is in front of the DVF. On the one hand, it enlarges the pelvic floor space for surgery, especially for patients with a narrow pelvis or obesity. On the other hand, it is beneficial for the surgeon to form good operative tension by pulling the resected peritoneal reflection. Subsequently, dissection is carried out in front of the DVF, and an 'inverted U-shaped' excision of the DVF approximately 0.5 cm above the base of the seminal vesicles is required for better preservation of the bilateral NVB and its branches. Finally, dissection is completed behind the DVF until a safe margin below the tumour is achieved. This approach helps to maintain the integrity of the proper fascia of the rectum and is suitable for tumours in any circumferential location. Our previous retrospective study[15–18] revealed that TME with PP-DVF was effective in protecting postoperative urogenital function with satisfactory oncological outcomes. However, there is a lack of randomised controlled trials to prove that the efficacy of TME with PP-DVF is equivalent to that with CP-DVF with respect to postoperative urogenital function.

Thus, we will conduct a prospective, multicentre, randomised trial to evaluate the effects of PP-DVF and CP-DVF during TME on postoperative urogenital function in male patients with low rectal cancer. In addition, surgical safety and oncological outcomes will also be evaluated. This study will provide high-grade evidence for the surgical approach of TME in patients with low rectal cancer.

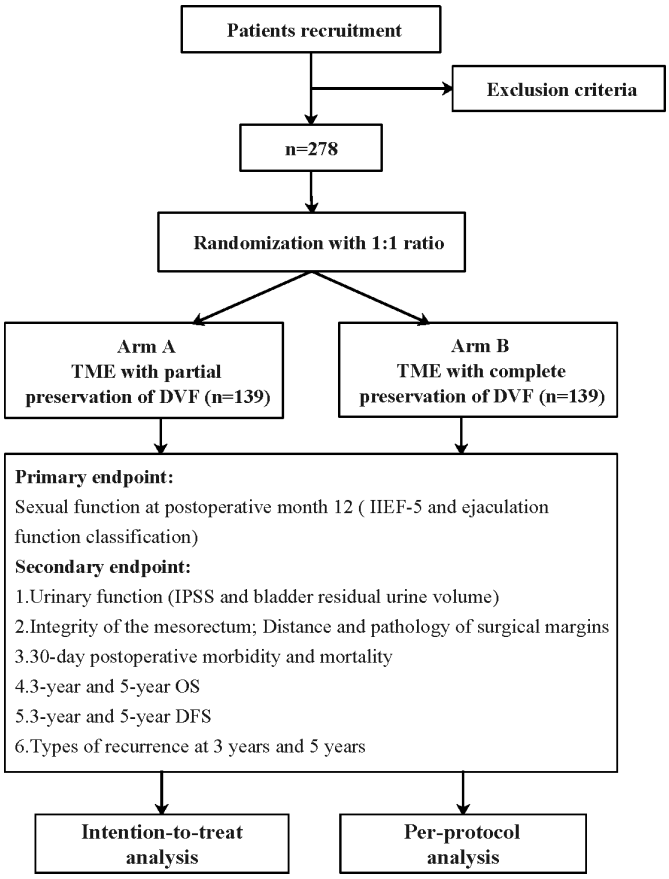

Figure 1 Flow chart of the study. DFS, disease-free survival; DVF, Denonvilliers' fascia; IIEF-5, a 5-item version of the International Erectile Function Index Questionnaire; IPSS, International Prostate Symptom Score; OS, overall survival; TME, total mesorectal excision.

METHODS AND ANALYSIS

Study description

This study is a prospective, multicentre, equivalent design, open-label randomised clinical trial that will recruit 278 male patients with low rectal cancer (139 patients in the PP-DVF group and 139 patients in the CP-DVF group) from 11 large-scale gastrointestinal medical centres in China. The study flow chart is shown in figure 1. The study is designed on the hypothesis that PP-DVF is similar to CP-DVF with respect to sexual function at postoperative month 12 (5-item version of the International Erectile Function Index Questionnaire[19] (IIEF-5) and ejaculation function classification) for male patients with cT1-3N0-2M0 or ycT1-3N0-2M0 low rectal cancer. Secondary outcomes include assessment of urinary function, surgical safety and oncological outcomes. Participating surgeons have rich experience with robotic or laparoscopic proctectomy and have performed over 50 TME procedures before. They were trained in surgical technique of intervention including PP-DVF and CP-DVF through training workshops before allowing participation and patient recruitment. To ensure the quality of intervention, at least 10 unselected, consecutive cases with PP-DVF or CP-DVF will be collected from each participating surgeons prior

to acceptance to the trial. Their surgical technique and radical resection skills have been recognised by an academic committee.

Participant recruitment and eligibility

Recruitment began in November 2020. Patients will be enrolled based on the following eligibility criteria:

Inclusion criteria

1. Man, 20≤age (years)≤70, with informed consent;
2. Pathological diagnosis of rectal adenocarcinoma;
3. Low rectal cancer (primary MRI showed that the lower margin of the tumour was ≤7 cm from the anal verge);
4. Preoperative staging of cT1-3N0-2M0 or ycT1-3N0-2M0 rectal cancer (American Joint Committee on Cancer (AJCC)-eighth edition);
5. Preoperative heart, lung, liver and kidney functions can be tolerated for surgery;
6. 6.Preoperative American Society of Anesthesiologists (ASA) grade I~III;
7. Undergoing elective TME surgery for colon-rectal or colon-anal anastomosis;
8. Normal preoperative genitourinary function, including erection function (IIEF-5 >21), ejaculation function classification (level I) and urinary function (International Prostate Symptom Score (IPSS) <8). (For patients undergoing neoadjuvant chemoradiotherapy (nCRT), the genitourinary function was assessed after nCRT and before surgery.)

Exclusion criteria

1. Simultaneous or heterogeneous (within 5 years) malignant tumours;
2. Patients with acute ileus, perforation, haemorrhage or other conditions requiring emergency surgical resection;
3. A history of pelvic and urinary major operation;
4. Severe mental illness;
5. Critical organ dysfunction, unbearable surgery;
6. Unstable angina, myocardial infarction, cerebral infarction or haemorrhage within 6 months;
7. Systemic corticosteroids or immunosuppressive medication history within 1 month;
8. With other diseases that need surgery;
9. Pre-existing true incontinence or severe stress urinary incontinence;
10. No sexual life or inability to cooperate with a physician to complete a functional evaluation;
11. The presence of contraindications for laparoscopic or robotic surgery.

Randomisation and blinding

Eligible patients will be randomised into the PP-DVF or CP-DVF group at a 1:1 ratio. Participants will be randomised using a block randomisation model (block size 6). Computer-generated, random-number tables will be prepared by an experienced statistician. After obtaining baseline data, allocation of treatment will be performed by the computer system, and allocation results will be provided to the surgeon in a concealed envelope the day before surgery. The patients, research assistants involved in data collection and follow-up, and data analysts will be blinded.

Treatment

Laparoscopic or robotic TME surgery will be performed in accordance with the Chinese Protocol of Diagnosis and Treatment of Colorectal Cancer (2020 edition)[20] and the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines for Rectal Cancer (Version 2, 2018).[21] All patients were evaluated by preoperative staging work-ups including a digital rectal examination, colonoscopy, chest radiography, endorectal ultrasound examination, abdominopelvic CT and pelvic MRI. To enable consistency in preoperative staging, dual reporting of images was used. The standardised MRI structural reporting for rectal cancer recommended by the national guidelines[20] was used in this study, including tumour size, the distance between the lower margin of the tumour from the anal verge, the distance of the tumour to the circumferential margin and so on. The clinical and pathological stages were determined according to the AJCC-8 tumour, node, metastases classification. Eligible patients were randomly assigned to the experimental group or the control group. To ensure the homogeneity and quality of surgery, unedited video recordings of each procedure will be stored for reference and mandatory intraoperative photographs of specific fields to verify PAN protection

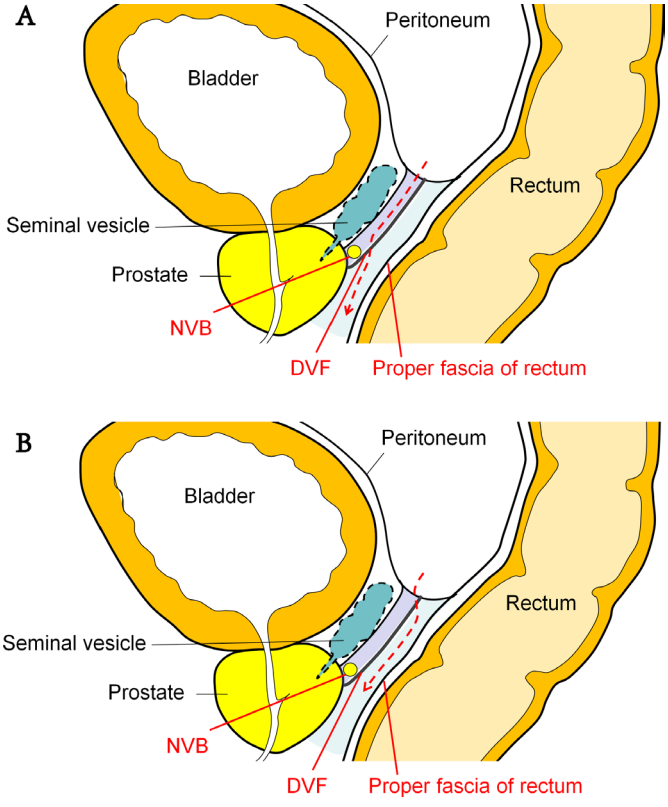

Figure 2 Surgical sketches. (A) Partial preservation of Denonvilliers' fascia (DVF); (B) complete preservation of DVF. NVB, neurovascular bundles.

Table 1 Schedule of enrolments, interventions and assessments

	Prerandomisation	Postrandomisation										
Time point	**Baseline**	**Surgery**	**POD5**	**3 month**	**6 month**	**9 month**	**12 month**	**15 month**	**18 month**	**21 month**	**24 month**	**30–60* month**
Screening for eligibility	※											
Informed consent	※											
Operation		※										
IIEF-5	※				※		※				※	
Ejaculation function classification	※				※		※				※	
I-PSS	※		※	※	※		※				※	
Bladder residual urine volume	※		※	※	※		※					
Physical examination	※			※	※	※	※	※	※	※	※	※
Tumour markers	※			※	※	※	※	※	※	※	※	※
Abdominal/pelvic ultrasound				※	※	※	※	※	※	※	※	※
MRI or CT scan of liver and pelvis	※						※				※	※
Colonoscopy†	※			※			※					※
Survival status				※	※	※	※	※	※	※	※	※

*Once every 6 months, with a colonoscopy every 1 year after surgery; if any abnormalities are present, review within 1 year; if no polyps are present, review within 3 years.
†If a preoperative colonoscopy fails to pass the location of the lesion, a colonoscopy will be performed 3 months after the surgery.
IIEF-5, A 5-item version of the International Erectile Function Index Questionnaire; I-PSS, International Prostate Symptom Score; POD, postoperative day.

will be obtained illustrating (1) the area of ligation of the inferior mesenteric artery, (2) the area of bilateral hypogastric nerve, (3) the location of dissection of the peritoneal reflection, (4) the excision level of the DVF, (5) the anterior rectal wall and DVF area and (6) the front and sides of the gross specimen.

Intervention of the experimental group: PP-DVF

The dissection will commence 1 cm above the peritoneal reflection (online supplemental video 1). Subsequently, dissection is carried out in front of the DVF, and an 'inverted U-shaped' excision of the DVF approximately 0.5 cm above the base of the seminal vesicles is required for better preservation of the bilateral NVB and its branches. Finally, dissection is completed behind the DVF until a safe margin below the tumour is achieved (figure 2A, online supplemental video 2).

Intervention of the control group: CP-DVF

After dissection 1 cm above peritoneal reflection, the dissection is performed behind the DVF until a safe margin below the tumour is achieved (figure 2B, online supplemental video 3). In this plane, the seminal vesicles are not visible and are covered with the thickened and bright DVF.

Data collection

We designed a case report form (CRF) for researchers to fill out the information of the patients during the study. When patients are enrolled in this study, two data managers staff members and one independent quality monitor will be assigned to collect relevant data, including demographic information, ASA score, laboratory tests (full blood count, blood biochemistry, tumour biomarkers, etc), imaging examination findings (CT or MRI), colonoscopy results, IIEF-5 and IPSS questionnaires, ejaculation function grading and bladder residual urine examination data. Perioperative data will be registered by scientific nurses and monitored by a quality monitor. After discharge, a 5-year follow-up is required. The follow-up and functional evaluation schedule for the study is shown in table 1. For patients with cT3/T4aN0M0 or cT1-4aN1-2M0 disease, nCRT will be used under the guidance of experienced oncologists. nCRT consists of a dose of 45–50.4 Gy/25–28-fraction radiotherapy and concurrent chemotherapy with capecitabine (825 mg/m^2 by mouth two times per day, 5–7 days a week, a total of 5 weeks). After nCRT and before surgery, only patients with a downstaging stage of ycT1-3 can be included in this study, but not ycT4. Surgery will be performed 8 weeks after the last dose of radiotherapy. For patients with nCRT or pathological tumour stage II or higher, adjuvant chemotherapy with a 6-month scheme of XELOX (oxaliplatin: 130 mg/m^2 intravenous drip d1; capecitabine: 1000 mg/m^2 by mouth two times per day d1–14, repeated every 21 days) will be performed. Adverse events during chemotherapy will be recorded on a CRF document. We use the Common Terminology Criteria for Adverse Events V.4.0 formulated by the National Institutes of Health National Cancer Institute to classify adverse events during adjuvant chemotherapy.[22]

Sample size

The sample size for this study was calculated based on the IIEF-5 scores at postoperative month 12. In our previous study, the mean IIEF-5 score of the CP-DVF procedure was 19.95 (SD: 4.95).[17] The corresponding score of the PP-DVF procedure was 16.63 (SD: 6.28).[12] According to the equivalent study design, the sample size was determined using a significance level (alpha) of 0.05 and a power (beta) of 90%. The equivalent threshold of 15% is clinically acceptable. PASS V.15.0 software was used to calculate sample sizes of 111 with a 1:1 ratio in each group. Considering a possible 20% rate of loss to the follow-up, 278 patients (139 patients in the PP-DVF group and 139 patients in the CP-DVF group) are needed to accomplish the goal of this study.

Statistical analysis

Continuous variables will be presented as the mean±SD, and categorical variables will be presented as numbers (percentages). Data with a skewed distribution will be presented as medians (IQRs). Student's t-test or the Mann-Whitney U test will be used to compare continuous variables. Categorical variables will be compared using χ^2 tests or Fisher's exact test. Survival data will be analysed according to the Kaplan-Meier method, and differences in survival will be tested by the log-rank test. All analyses will be conducted on intention-to-treat and per-protocol bases. A two-sided $p<0.05$ is set for significance. Statistical analysis will be performed using SPSS V.25.0 software (SPSS).

Patient and public involvement statement

The patients and the public will not be involved in the design, conduct, reporting and dissemination of the study. We will disseminate the trial results via peer-reviewed journals and conference presentations rather than notifying every single patient. Indicators of subjective feelings, such as questionnaires about the IIEF-5 and IPSS, will be acquired by patients' self-report.

Ethics and dissemination

This trial has been approved by the Institutional Review Board of Fujian Medical University Union Hospital (2020YF016-01). We have registered the study on http://www.chictr.org.cn. Written informed consent (online supplemental appendix 1) will be obtained from all eligible participants before enrolment. Trial results will be disseminated via peer-reviewed scientific journals and conference presentations.

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Contributors All authors made substantial contributions to the intellectual content of this paper. PC and YH conceived and designed this study. ZZ and DY are the

co-first authors who participated in the trial design and wrote this article. XW and XL contributed to the study design and interpreted the results and commented on drafts of the paper.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

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REFERENCES

1 Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. *CA Cancer J Clin* 2019;69:7–34.
2 Heald RJ, Husband EM, Ryall RD. The mesorectum in rectal cancer surgery--the clue to pelvic recurrence? *Br J Surg* 1982;69:613–6.
3 Heald RJ, Ryall RDH. Recurrence and survival after total mesorectal excision for rectal cancer. *The Lancet* 1986;327:1479–82.
4 Dulskas A, Miliauskas P, Tikuisis R, *et al*. The functional results of radical rectal cancer surgery: review of the literature. *Acta Chir Belg* 2016;116:1–10.
5 Hendren SK, O'Connor BI, Liu M, *et al*. Prevalence of male and female sexual dysfunction is high following surgery for rectal cancer. *Ann Surg* 2005;242:212–23.
6 Heald RJ, Moran BJ, Brown G. Optimal total mesorectal excision for rectal cancer is by dissection in front of Denonvilliers' fascia. *Br J Surg* 2004;1:121–3.
7 Bonjer HJ, Deijen CL, Abis GA, *et al*. A randomized trial of laparoscopic versus open surgery for rectal cancer. *N Engl J Med* 2015;372:1324–32.
8 Sun V, Grant M, Wendel CS, *et al*. Sexual function and health-related quality of life in long-term rectal cancer survivors. *J Sex Med* 2016;13:1071–9.
9 Schmiegelow AFT, Broholm M, Gögenur I, *et al*. Evaluation of sexual and urinary function after implementation of robot-assisted surgery for rectal cancer: a single-center study. *Surg Laparosc Endosc Percutan Tech* 2016;26:141–5.
10 Kinugasa Y, Murakami G, Uchimoto K, *et al*. Operating behind Denonvilliers' fascia for reliable preservation of urogenital autonomic nerves in total mesorectal excision: a histologic study using cadaveric specimens, including a surgical experiment using fresh cadaveric models. *Dis Colon Rectum* 2006;49:1024–32.
11 Fang J, Zheng Z, Wei H. Reconsideration of the anterior surgical plane of total mesorectal excision for rectal cancer. *Dis Colon Rectum* 2019;62:639–41.
12 Wei B, Zheng Z, Fang J. Effect of Denonvilliers' fascia preservation versus resection during laparoscopic total mesorectal excision on postoperative urogenital function of male rectal cancer patients: initial results of Chinese Puf-01 randomized clinical trial. *Ann Surg* 2020.
13 Ghareeb WM, Wang X, Chi P, *et al*. The 'multilayer' theory of Denonvilliers' fascia: anatomical dissection of cadavers with the aim to improve neurovascular bundle preservation during rectal mobilization. *Colorectal Dis* 2020;22:195–202.
14 Muraoka K, Hinata N, Morizane S, *et al*. Site-Dependent and interindividual variations in Denonvilliers' fascia: a histological study using donated elderly male cadavers. *BMC Urol* 2015;15:42.
15 Zheng Z, Wang X, Huang Y, *et al*. Alternative anterior surgical plane of total mesorectal excision for rectal cancer: partial preservation of Denonvilliers' fascia. *Tech Coloproctol* 2021. doi:10.1007/s10151-021-02549-x. [Epub ahead of print: 25 Nov 2021].
16 Chi P, Wang XJ. [Membrane Anatomy: Motivation to Promote Precise Laparoscopic and Robot Colorectal Surgery]. *Zhonghua Wei Chang Wai Ke Za Zhi* 2019;5:406–12. doi:10.3760/cma.j.issn.1671-0274.2019.05.002
17 Huang ZK, Chi P, Huang Y. [Robotic Versus Laparoscopic Total Mesorectal Excision with Partial Preservation of Denonvilliers Fascia: A Comparative Study of Short-Term Efficacy and Urinary and Erectile Function]. *Zhonghua Wei Chang Wai Ke Za Zhi* 2021;4:327–34. doi:10.3760/cma.j.cn.441530-20200724-00444
18 Wang X-J, Chi P, Lin H-M, *et al*. A scoring system to predict inferior mesenteric artery lymph node metastasis and prognostic value of its involvement in rectal cancer. *Int J Colorectal Dis* 2014;29:293–300.
19 Rosen RC, Riley A, Wagner G, *et al*. The International index of erectile function (IIEF): a multidimensional scale for assessment of erectile dysfunction. *Urology* 1997;49:822–30.
20 [Chinese Protocol of Diagnosis and Treatment of Colorectal Cancer (2020 Edition)]. *Zhonghua Wai Ke Za Zhi* 2020;8:561–85. doi:10.3760/cma.j.cn112139-20200518-00390
21 Benson AB, Venook AP, Al-Hawary MM, *et al*. Rectal cancer, version 2.2018, NCCN clinical practice guidelines in oncology. *J Natl Compr Canc Netw* 2018;16:874–901.
22 Institute NC. Common Terminology Criteria for Adverse Events (Ctcae) V4.0[Eb/Ol]. Available: https:// Ctep. Cancer. Gov/ Protocoldevelopment/ Electronic_Applications/ Ctc. Htm [Accessed 14 Jun 2010].